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Management of Asthma in Children

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1. Introduction

Asthma is defined as a chronic inflammatory disorder of the lower airways resulting in an obstruction of airflow, which may be completely or partially reversed with or without specific therapy. The inflammation is an interaction between various cells and cytokines. Asthmatic patients have recurrent or persistent bronchospasm, which causes symptoms e.g. wheezing, breathlessness, chest tightness, and cough, particularly at night or after exercise.

Chronic airway inflammation causes bronchial hyperresponsiveness (BHR), which is defined as the inherent tendency of the airways to narrow in response to various stimuli (eg, environmental allergens and irritants).[1]

2. Epidemiology

The prevalence of childhood asthma is 10 times higher in developed countries (UK, US, Australia and New Zealand) than in developing countries. Low income population in urban areas have higher prevalence rate than other groups (ISAAC).[2-6]

Asthma in children accounts for more school absences and more hospitalizations than any other chronic illness and is the most common diagnosis at admission.[7]

300 million individuals worldwide have asthma. Prevalence of asthma is increasing, especially in children. WHO has estimated that 15 million disability-adjusted life-years are lost and 250,000 asthma deaths are reported worldwide.[8]

3. Pathophysiology

The interplay between environment and genetic factors lead to airway inflammation, which result in functional and structural changes in the airways in the form of bronchospasm, mucosal edema, and mucus plugs, which increases resistance to airflow and decreases expiratory flow rates. Although over-distention helps maintain airway patency, and improves expiratory flow; it also alters pulmonary mechanics and increases the work of breathing, resulting ultimately in alveolar hypoventilation.[9]

Changes in airflow resistance, uneven distribution of air, and alterations in circulation (mainly vasoconstriction from increased intra-alveolar pressure due to hyperinflation) lead to ventilation-perfusion mismatch. [10-13]

Patients with acute asthma exacerbations in the **early stages**, have hypoxemia in the absence of carbon dioxide retention, as increases in alveolar ventilation prevents hypercarbia. [14]

If obstruction continues and ventilation-perfusion mismatch worsens, carbon dioxide retention and respiratory alkalosis occur. **Later**, the increased work of breathing, increased oxygen consumption, and increased cardiac output lead to metabolic acidosis. Respiratory failure leads to respiratory acidosis. [15-16]

4. Inflammation of the airways

The inflammatory process in the airways causes increased BHR, which leads to bronchospasm and typical symptoms of wheezing, shortness of breath, and coughing after exposure to allergens, environmental irritants, viruses such as RSV, Rhinovirus a.o., cold air, or exercise. [17]

Lymphocytes play a central role in the pathogenesis of asthma. Airway inflammation may represent a mis-balance between two "opposing" populations of T helper (Th) lymphocytes. Two types of Th lymphocytes have been characterized: Th1 and Th2. Th1 cells produce interleukin (IL)-2 and interferon-a (IFN-a), which are critical in cellular defense mechanisms in response to infection. Th2, in contrast, generates a family of cytokines (interleukin-4 [IL-4], IL-5, ILL6, IL-9, and IL-13) that can mediate allergic inflammation.[18-22]

Cytokines play a key role in orchestrating the chronic inflammation of asthma and other obstructive airways disease recruiting, activating, and promoting the survival of multiple inflammatory cells in the respiratory tract. Cytokines are classified into lymphokines (cytokines that are secreted by T cells and regulate immune responses), proinflammatory cytokines (cytokines that amplify and perpetuate the inflammatory process), growth factors (cytokines that promote cell survival and result in structural changes in the airways), chemokines (cytokines that negatively modulate the inflammatory response).23

Epithelial cells in the airways play an important role in orchestrating the inflammation of asthma through the release of multiple cytokines. Th2 cells orchestrate the inflammatory response in asthma through the release of IL-4 and IL-13 (which stimulate B cells to synthesize IgE), IL-5 (which is necessary for eosinophilic inflammation), and IL-9 (which stimulates mast cell proliferation). Mast celles are thus orchestrated by several interacting cytokines and play an important role in asthma through the release of the bronchoconstrictor mediator histamine, cysteinyl-leukotrienes (Cys-LTs), and PGD2)

Bronchial biopsies from asthmatics show infiltration with eosinophils, activated mast cells, and T cells that are predominantly Th2 cells. There are characteristic structural changes, with collagen deposition under the epithelium (also described as basement membrane thickening) and increased airway smooth muscle as a result of hyperplasia hypertrophy. There is also an increase in the number of blood vessels angiogenesis) as well as mucus hyperplasia.24

In patients with asthma, there is an increase in the number of CD4+ Th cells in the airways, which are predominantly of the Th2 subtype. Th2 cells are characterized by secretion of IL-4, IL-5, IL-9, and IL-13. The transcription factor GATA-binding protein 3(GATA3) is crucial for the differentiation of uncommitted naïve T cells into Th2 cells and regulates the secretion of Th2 cytokines. There is an increase in the number of GATA3+ T cells in the airways of stable asthmatic subjects. Nuclear factor of activated Tcells (NFAT) is a T-cell-specific transcription factor and enhances the transcriptional activation of the IL4 promoter by GATA3. Finally, IL-33, a member of the IL-1 family of cytokines, promotes differentiation of Th2 cells by translocating to the nucleus and regulating transcription through an effect on chromatin structure, but it also acts as a selective chemoattractant of Th2 cells.25

IL-4 plays a critical role in differentiation of Th2 cells from uncommitted Th0 cells and may be important in initial sensitization to allergens. It is also important for isotype switching of B cells from producers of IgG to producers of IgE. IL-12 mimics IL-4 in inducing IgE secretion and causing structural changes in the airways but does not play a role in promoting Th2 cell differentiation.

IL-5 plays a key role in inflammation mediated by eosinophils, since it is critically involved in the differentiation of eosinophils from bone marrow precursor cells and also prolongs eosinophils survival. Systemic and local administration of IL-5 to asthmatic patients results in an increase in circulating eosinophils and CD34+ eosinophil precursors.

The transcription factor T-bet is crucial for the Th1 cell differentiation and secretion of the Th1-type cytokine IFN-γ. Consistent with the prominent role of Th2 cells in asthma, T-bet expression is reduced in T cells from the airways of asthmatic patients compared with airway T cells from nonasthmatic patients.

Type 1 IFNs (IFN-α and IFN-β) and type III IFNs (IFN-λ) play an important role in innate immunity against viral infections, but IFN-β and IFN-λ show reduced expression in epithelial cells of asthmatic patients and are associated with increased rhinovirus replication, which may predispose these patients to viral exacerbations of asthma.

IL-12 plays an important role in differentiating the activating Th1 cells and is produced by activated macrophages, DCs, and airway epithelial cells. IL-12 induces T cells to release IFN-γ, which regulates the expression of IL-12Rβ2 and so maintains the differentiation of Th1 cells, whereas IL-4 suppresses IL-12Rβ2 expression and thus antagonizes Th1 cell differentiation.26

Thymic stromal lymphopoietin. Thymic stromal lymphopoietin (TSLP) is a cytokine belonging to the IL-7 family that shows a marked increase in expression in airway epithelium and mast cells of asthmatic patients. TSLP is released from airway epithelial cells, and its synergistic interaction with IL-1β and TNF-α results in the release of Th2 cytokines from mast cells independently of T cells. TSLP also plays a key role in programming airway DCs to release the Th2 chemoattractants CCL17 and CCL2 and thus is important in recruiting Th2 cells to the airways.

GM-CSF plays role in the differentiation and survival of neutrophils, eosinophils, and macrophages and has been implicated in asthma. Its receptor comprises and α-chain that is specific for the receptor for GM-CSF and a β-chain that is also part of the receptors for IL-3 and IL-5. GM-CSF is secreted predominantly by macrophages, epithelial cells, and T cells in response to inflammatory stimuli. Airway epithelial cells of asthmatic patients strongly express GM-CSF, which may condition DCs to direct Th2 immunity and to prolong the survival of eosinophils.27

Neutrophins are cytokines that play an important role in the function, proliferation, and survival of autonomic nerves. In sensory nerves, neutrophins increase responsiveness and expression of tachykinins. Nerve growth factor (NGF) may be produced by mast cells, lymphocytes, macrophages, and eosinophils as well as structural cells, such as epithelial cells, fibroblasts, and airwy smooth muscle cells.

In recent years more focus on **"the hygiene hypothesis",** which is in a simplified way, a cytokine imbalance resulting in a dramatic increase in asthma prevalence in Westernized countries. This hypothesis is based on the concept that the immune system of the newborn is skewed toward Th2 cytokine generation (mediators of allergic inflammation). Environmental stimuli such as infections activate Th1 responses and bring the Th1/Th2 relationship to an appropriate balance.[28-30]

A series of epidemiological studies in Europe, Canada, and Australia showed reduced prevalence of asthma and allergy among farmers' children compared to non-farmers' children. Stable visits early in life and consumption or raw cow's milk were suggested as the main factors of the farming environment conferring protection against atopic diseases. These results have been seen as an extension of the 'hygiene hypothesis', since a farm environment provides an enormous habitat for microorganisms.

Pattern-recognition receptors (RPR) of the innate immune system, such as toll-like receptors (TLR) or CD14, recognize LPS (lipopolysaccharide), a component of the outer membrane of gram-negative bacteria, and other nonviable environmental compounds. Activation of PRR signaling pathways initiates regulatory mechanisms which in turn modulate the adaptive immune response. Interestingly, recently it has been shown that farmers' children express higher levels of PRR than children from non-farming families suggesting that innate immune mechanisms are involved in the allergy-protective effect of the farming environment.

For various genetic loci, i.a. the CD14 an association with the occurrence of atopic diseases have been described. However, studies investigating the same genetic variants in other populations often failed to reproduce the original results.

Gene environment interactions have been found for several genetic polymorphisms in PRR genes.

Several studies indicated higher gene expression of CD14,TLR 2, and TLR4 in farmers' children compared to non-farmers' children. Mainly prenatal factors accounted for these differences. Expression of CD14, TLR2, TLR4 with the number of farm animal species the mother had contact with during pregnancy, which probably serves as proxy for an increasing variation in microbial exposure. Children of mothers who worked on the farm during pregnancy were less sensitized at school age to common inhalant and food allergens than children of unexposed mothers. However development of clinical symptoms of atopic disease seemed to depend on exposures that occurred postnatally.[33]

Evidence suggests that the prevalence of asthma is less in children who experience:

- Less frequent use of antibiotics
- Exposure to other children (eg, presence of older siblings and early enrollment in childcare)
- Rural living
- Certain infections (Mycobacterium tuberculosis, measles, or hepatitis A)

On the contrary, the absence of these lifestyle events is associated with the persistence of a Th2 cytokine pattern (Allergy).

The genetic background of a child, with a cytokine imbalance toward Th2, sets the stage to promote the production of immunoglobulin E (lgE) antibody to key environmental antigens (e.g., cockroaches, dust mites, cats and alternaria). Therefore, a gene-by-environment interaction occurs in which the susceptible host is exposed to environmental factors that are capable of generating IgE, and sensitization.[34]

Allergic inflammation may be the result of an excessive expression of Th2 cytokines. Recent studies have suggested the possibility that the loss of normal immune balance arises from a cytokine dysregulation in which Th1 activity in asthma is diminished .

5. Genetic factors and asthma

Recent research studies have identified phenotypes (clusters) of genes which could predispose individuals to asthma. Cluster 1 patients have early-onset atopic asthma and preserved lung function but increased medication requirements (29% on three or more medications) and health care utilization. [35]

Genetic Factors

Genome-wide linkage studies and case-control studies have identified 18 genomic regions and more than 100 genes associated with allergy and asthma in 11 different populations. A recent genome-wide association study identified a new gene, ORMDL3, that exhibited a highly significantly association with asthma ($p < 10\text{-}12$) (for single nucleotide polymorphism rs8067378, odds ratio 1.84, 95% confidence interval 1.43-2.42) a finding that has now been replicated in several populations.

Several studies identified candidate genes in a pathway that initiates type 2 helper T-cell (Th2) inflammation in response to epithelial damage and points to other candidate genes that may act in a pathway that down-regulates airway inflammation and remodeling. Our study also shows that asthma is heterogeneous: later-onset cases are influenced more by the MHC (major histocompatibility complex) than are childhood-onset cases. There is a strong and specific effect of the chromosome 17q locus on childhood-onset disease.[37]

SNPs at the chromosome 17q21 locus associated with asthma are also strongly associated with variation in the expression of ORMDL3 and GSDMB.

There is an association between SNPs flanking IL33 on chromosome 9 and atopic asthma. [38]

The locus chromosome at 2, implicating 1L1RL1 and IL 18R1 is also associated with asthma. The effect at this locus has been attributed to IL 1RL1 (encoding the receptor for interleukin) [6] and synergizes with IL 12 to induce the production of interferon-y and to promote Th1 responses. The expression of IL 18R1 is also concentrated within the respiratory epithelium.[39]

SMAD3 is a transcriptional modulator activated by transforming growth factor β, a polypeptide that controls proliferation, differentiation, and other functions in many cell types, including regulatory T cells. [40]

HLA-DQ was the first identified asthma susceptibility locus. Extended haplotypes encompassing HLA-DQ and HLA-DR have been studied for their effects on specific allergen sensitization and on the formation of tumor necrosis factor and related gene products.

Two other genes, SLC22A5 and RORA. SLC22A5 encodes a carnitine transporter and, like ORMDL3/GSDMB and IL18R1/IL1RL1.[41]

Cluster 2 comprises mostly older obese women with late-onset non-atopic asthma, moderate reductions in pulmonary function, and frequent oral corticosteroid use to manage exacerbations. Cluster 3 and cluster 4 patients have severe airflow obstruction with bronchodilator responsiveness but differ in to their ability to attain normal lung function, age of asthma onset, atopic status, and use of oral corticosteroids. [36]

6. Specific and non-specific triggers

Specific immune-response to triggers entails 2 types of bronchoconstrictor responses to allergens: early and late. [42]

Early asthmatic responses occur via IgE-induced mediator release from mast cells within minutes of exposure and last for 20-30 minutes. [43-45]

William et al found an increase rates of sensitization to indoor and outdoor aeroallergens throughout childhood. He also found different aeroallergens to be prominent at different ages. For example, dogs and cats were the most likely sensitizers in children younger than 4, whereas dust mites and trees were the most prominent in older children and adolescents.[46]
There was a relatively high rate of tree sensitization in the children less than 4 years of age.
The same study found that 57.2% of the referred patients who under SPT were sensitized to at least 1 of the studied aeroallergens, 51.3% of patients were sensitized to at least 1 indoor aeroallergen, and 38% were sensitized to at least 1 outdoor aeroallergen.[47-49]
Cat, dogs, and dust mites are the predominant sensitizers in younger children, whereas trees and dust mites are the most prevalent sensitizers in older children and adolescents. In contrast to grass and ragweed tree sensitization is much more common than expected in very young children.[50]

Late asthmatic responses occur 4-12 hours after antigen exposure and result in more severe symptoms that can last for hours and contribute to the duration and severity of the disease. Inflammatory cell infiltration and inflammatory mediators play a role in the late asthmatic response. Allergens can be foods, household inhalants (eg, animal allergens, molds, fungi, cockroach allergens, dust mites), or seasonal outdoor allergens (eg, mold spores, pollens, grass, trees).

Non-specific response e.g. tobacco smoke, cold air, chemicals, perfumes, paint odors, hair sprays, air pollutants, and ozone can initiate BHR by inducing inflammation. [9]

Sudden changes in ambient temperature, barometric pressure, and the quality of air (eg, humidity, allergen and irritant content) can also induce asthma exacerbations.[10]

Exercise can trigger an early asthmatic response. Different mechanisms are hypothesized to play a role. Heat and water loss from the airways can increase the osillolarity of the fluid lining the airways and result in mediator release. Cooling of the airways results in congestion and dilatation of bronchial vessels. During the rewarming phase after exercise, the changes are magnified because the ambient air breathed during recovery is warm rather than cool.

Emotional factors are sometimes incriminate to trigger asthma exacerbation (stress, emotional upsets a.o.)

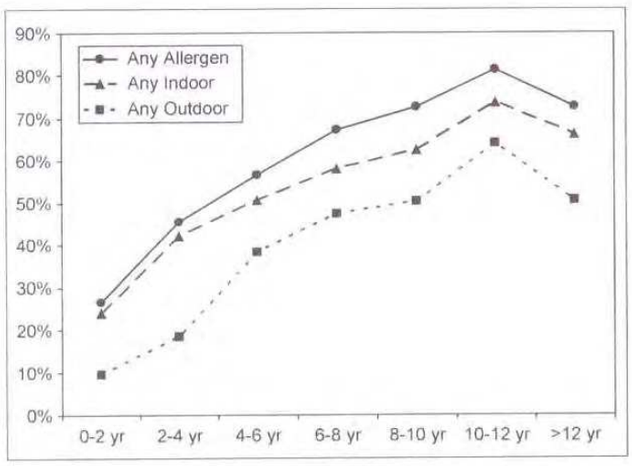

Figure 1. Age-specific prevalence of sensitization[a]
▲, Sensitization to at least 1 of the aeroallergens studied; ●, sensitization to at least 1 of the indoor aeroallergens (cats, dogs, dust mites, mice, cockroaches); ■, sensitization to at least 1 of the outdoor aeroallergens (trees, grass, ragweed).

Table 2. Prevalence of Positive Skin Prick Test for Each Allergen (All Ages)[a]

	Indoor Allergens					Outdoor Allergens		
Age (years)	Mice	Roaches	Dogs	Cats	Mites	Trees	Grass	Weeds
0-2	3.2 (93)	3.6 (138)	15.5 (174)	9.2 (174)	8.2 (195)	7.8 (103)	1.0 (98)	1.0 (97)
2-4	8.1 (235)	10.9 (239)	21.0 (271)	22.5 (267)	22.3 (287)	17.1 (252)	2.8 (246)	5.7 (245)
4-6	8.3 (206)	8.8 (205)	25.0 (216)	33.3 (222)	37.2 (231)	35.3 (221)	9.3 (215)	17.9 (218)
6-8	10.9 (184)	14.2 (183)	31.1 (190)	37.0 (189)	41.9 (191)	46.6 (191)	10.1 (189)	20.9 (187)
8-10	5.6 (142)	15.8 (139)	28.4 (148)	41.1 (146)	47.9 (140)	46.6 (148)	19.6 (143)	23.6 (144)
10-12	13.5 (111)	19.8 (111)	26.5 (113)	48.2 (110)	53.1 (113)	56.4 (110)	28.8 (111)	34.2 (111)
>12	10.4 (182)	22.2 (180)	23.0 (187)	38.5 (187)	56.8 (185)	45.2 (188)	21.7 (184)	24.3 (185)
Total	8.8 (1153)	13.3 (1195)	24.0 (1299)	31.3 (1295)	35.6 (1342)	35.8 (1213)	12.4 (1186)	17.7 (1187)

7. Gastroesophageal reflux

The presence of acid in the distal esophagus, mediated via vagal or other neural reflexes, can significantly increase airway resistance and airway reactivity.

8. Upper respiratory tract: conditions

Inflammatory conditions of the upper airways (eg, allergic rhinitis, sinusitis, or chronic and persistent infections) must be treated before asthmatic symptoms can be completely controlled.

9. Circadian rhythm

Circadian variation in lung function and inflammatory mediator release in the circulation and airways (including parenchyma) have been demonstrated to explain nocturnal asthma. Other factors, such as allergen exposure and posture-related irritation of airways (eg, gastroesophageal reflux, sinusitis), can also play a role. In some cases, abnormalities in CNS

control of the respiratory drive may be present, particularly in patients with a defective hypoxic drive and obstructive sleep apnea. [51]

It is well known that there is a circadian variation in asthma severity and exacerbation.
Wheezing, cough and dyspnea are worse during the late night and early morning hours[3]. Most dyspneic episodes occurring nocturnally, with a 50-fold increase in the number of attacks between 4 am and 5 am compared with the number of attacks between 4 pm and 5 pm.[4] Objective indicators of disease severity correlate closely with subjective dyspnea PEFR begins declining rapidly at midnight, and at 4 am is between 8% and 40% below its mean 24-hour value at 9 am. The PEFR then increases sharply and reaches its mean 24 hour value at 8 am.[5] Normal subjects also show circadian changes in airflow, with mild nocturnal bronchoconstriction, although the variation is far less pronounced than that seen in asthmatic subjects.[52]
The pathophysiology of nocturnal asthma exacerbation is not completely understood and appears to be multifactorial. Plasma cortisol levels vary markedly, reaching a nadir at midnight and peaking at 8 am. Serum histamine levels peak dramatically at about 4 am, dropping to baseline levels by 8 am. Plasma cyclic AMP(cAMP) levels reaches a nadir at 4 am, as do the density and responsiveness of beta-adrenergic receptors located on circulating leukocytes. A nocturnal increase in vagal tone has been described. All of these factors appear to play a role in destabilizing the inflammatory environment of the airways at night. Additionally, sleep-induced oxygen dessaturation, gastroesophageal reflux, and body temperature decline during sleep may all predispose to nocturnal airway hyperresponsiveness.[55-53]
The circadian nature of asthma has led to the argument that nocturnal presentation of asthma is marker of more severe disease, warranting more aggressive therapy and lower threshold for hospitalization than for other asthmatic patients. Data demonstrating increased asthma mortality between midnight and 4 am, although limited to inpatient settings, appear to support this argument. However, some studies of asthmatic patients in the emergency department failed to validate this hypothesis. Several studies however demonstrate no significant disease severity between asthmatic patients who presented during late night/early-morning hours.[58-56]

10. Asthma outcome

Children with mild asthma who are asymptomatic between attacks are likely to improve and be symptom-free later in life.

Children with asthma appear to have less severe symptoms as they enter adolescence, but half of these children continue to have asthma. Asthma has a tendency to remit during puberty, with a somewhat earlier remission in girls. However, compared with men, women have more BHR. [59]

Of infants who wheeze with URTIs, 60% are asymptomatic by age 6 years. However, children who have asthma (recurrent symptoms continuing at age 6 years) have airway reactivity later in childhood. Some findings suggest a poor prognosis if asthma develops in children younger than 3 years, unless it occurs solely in association with viral infections. [60-62]

Individuals who have asthma during childhood have significantly lower forced expiratory volume in 1 second (FEV1), higher airway reactivity, and more persistent bronchospastic symptoms than those with infection-associated wheezing.

11. Patient education

11.1 Pediatrician and/or asthma educator should instruct

Patient and parent on how to use medications and devices (eg, spacers, nebulizers, metered-dose inhalers [MDIs]). The patient's MOI technique should be assessed on every visit.[63]

Instruction should also includes the use of medications, precautions with drug and/or device usage, monitoring symptoms and their severity (peak flow meter reading), and identifying potential adverse effects and necessary actions. [64]

Parents should understand that asthma is a chronic disorder with acute exacerbations; hence, continuity of management with active participation by the patient and/or parents and interaction with asthma care medical personnel is important. Adherence to treatment is the key to full control of symptoms including nocturnal and exercise-induced symptoms. Emphasize the importance of adherence to treatment.[65]

Parents caregiver and teachers should expect the child to participate in recreational activities and sports and to attend school as usual. [66]

12. Differential diagnoses

12.1 Problems to be considered include the following

- Vascular ring
- Vocal cord dysfunction
- Tracheobronchomalacia
- Pulmonary edema
- Gastroesophageal Reflux
- Bronchopulmonary Dysplasia
- Bronchiectasis
- Aspiration Syndromes
- Airway Foreign Body
- Allergic Rhinitis
- Aspergillosis
- Cystic Fibrosis
- Primary Ciliary Dyskinesia [67]

13. Clinical presentation

13.1 History is very important in asthma the clinician should confirm

- Airflow obstruction or symptoms are at least partially reversible
- Episodic symptoms of airflow obstruction are present
- Alternative diagnoses are excluded

Obtaining a good patient history is crucial when diagnosing asthma and excluding other causes, symptoms, aggravating factors and co-existing conditions should be asked.

- Shortness of breath
- Cough
- Wheezing
- Cough at night or with exercise
- Chest tightness
- Sputum production
- Onset and duration
- Perennial, seasonal, or both
- Daytime or nighttime

- Continuous or intermittent
- Exercise
- Viral infections
- Irritants (eg, smoke exposure, chemicals, vapors, dust)
- Environmental allergens
- Changes in weather
- Emotions
- Stress
- Foods
- Home environment (eg, carpets, pets, mold)
- Drugs (eg, aspirin, beta blockers)
- Rhinitis
- Sinusitis
- Gastroesophageal reflux disease (GERD)
- Thyroid disease

Vascular rings are unusual congenital anomalies that occur early in the development of the aortic arch and great vessels. The primary symptomatology associated with vascular rings relates to the structure that are encircled by the ring, chiefly the trachea, large airways and esophagus.

PERINATAL AND FAMILY HISTORY	POSSIBLE DIAGNOSIS
Symptoms present from birth or perinatal lung problem	Cystic fibrosis; chronic lung disease of prematurity; ciliary dyskinesia; developmental anomal
Family history of unusual chest disease	Cystic fibrosis; neuromuscular disorder
Severe upper respiratory tract disease	Defect of host defence; ciliary dyskinesia
Symptoms and signs	
Persistent moist cough	Cystic fibrosis; bronchiectasis; protracted bronchitis; recurrent aspiration; host defence disorder; ciliary dyskinesia
Excessive vomiting	Gastroesophageal reflux (+-aspiration)
Dysphagia	Swallowing problems (+- aspiration)
Breathlessness with light-headedness and peripheral tingling	Hyperventilation/panic attacks
Inspiratory stridor	Tracheal or laryngeal disorder
Abnormal voice or cry	Laryngeal problem
Focal signs in chest	Developmental anomaly; post-infective syndrome; bronchiectasis; tuberculosis
Finger clubbing	Cystic fibrosis; bronchiectasis
Failure to thrive	Cystic fibrosis; host defense disorder; gastroesophageal
Other conditions	
Transient infant wheezing	Onset in infancy; no associated atopy associated with parental smoking
Inhaled foreign body	Suddent onset

Differential Diagnosis of Asthma in Children 5 years and younger
Infections: • Recurrent Respiratory tract infections • Chronic rhino-sinusitis • Tuberculosis.
Congenital problems: • Tracheomalacia • Cystic Fibrosis • Bronchopulmonary dysplasia • Congenital malformation causing narrowing of the intratoracic airways. • Primary ciliary dyskinesia syndrome • Immune deficiency • Congenital heart disease
Mechanical Problems • Foreign body aspiration • Gastroesophageal reflux
Adopted from GINA Guide 2011

The family history should include any history of asthma, allergy, sinusitis, rhinitis, eczema, or nasal polyps in close relatives, and the social history should cover factors that may contribute to non adherence of asthma medications, as well as any illicit drug use.[68-72]

Physical findings vary with the absence or presence of an acute episode and its severity.

A patient with mild asthma may have normal findings on physical examination. Patients with more severe asthma are likely to have signs of chronic respiratory distress and chronic hyperinflation.

Signs of atopy or allergic rhinitis, such as conjunctival congestion and inflammation, allergic shiners, a transverse crease on the nose due to constant rubbing associated with allergic rhinitis, and pale nasal mucosa covered with transparent mucus due to allergic rhinitis, may be present.

The anteroposterior diameter of the chest may be increased because of hyperinflation. Hyperinflation may also cause an abdominal breathing pattern.

Lung examination may reveal prolonged expiratory phase, expiratory wheezing, coarse crackles, or unequal breath sounds.

Clubbing of the fingers is not a usual feature of asthma and indicates a need for more extensive evaluation and work-up to exclude other conditions, such as cystic fibrosis.[73-77]

A child with an acute episode may reveal different findings in mild, moderately severe, and severe episodes and in status asthmaticus with imminent respiratory arrest.

13.2 Mild episode asthma reveals

- Accessory muscles of respiration are not used
- Increased respiratory rate

- The heart rate is less than 100 beats per minute
- Auscultation of chest reveals moderate wheezing, which is often end expiratory
- Pulsus paradoxus is not present
- Oxyhemoglobin saturation with room air is greater than 95%

13.3 Moderately severe asthma include the following

- Increased respiratory rate
- Accessory muscles of respiration typically are used
- Suprasternal retractions are present
- The heart rate is 100-120 beats per minute
- Loud expiratory wheezing can be heard
- Pulsus paradoxus may be present (10-20 mm Hg)
- Oxyhemoglobin saturation with room air is 91-95%

13.4 Severe asthma include the following:

- The respiratory rate is often greater than 30 breaths per minute
- Accessory muscles of respiration are usually used
- Suprasternal retractions are commonly present
- The heart rate is greater than 120 beats per minute
- Loud biphasic (expiratory and inspiratory) wheezing can be heard
- Pulsus paradoxus is often present (20-40 mm Hg)
- Oxyhemoglobin saturation with room air is less than 91 %.

13.5 Status asthmaticus may include the following

- Paradoxical thoracoabaominal movement
- Wheezing may be absent (in patients with the most severe airway obstruction)
- Severe hypoxemia may manifest as bradycardia
- Pulsus paradoxus may disappear; this finding suggests respiratory muscle fatigue

14. Workup

Spirometry is indicated in children >6 years, as younger children < 6 years are unable to perform spirometry, unless modern techniques such as measurement of airway resistance using oscillometry is applied.

In a typical case, an obstructive defect is present in the form of normal forced vital capacity (FVC), reduced forced expiratory volume in 1 second (FEV1), and reduced forced expiratory flow more than 25-75% of the FVC (FEF 25-75). The flow-volume loop can be concave. Documentation of reversibility of airway obstruction after bronchodilator therapy is essential to the definition of asthma. FEF 25-75 is a sensitive indicator of obstruction and may be the only abnormality in a child with mild disease.

In an outpatient or office setting, measurement of the peak flow rate by using a peak flow meter can provide useful information about obstruction in the large airways.

	Daytime symptoms between exacerbations	Night-time symptoms between exacerbations	Exacerbations	PEF or FEV1*	PEF variability**
Infrequent intermittent	Nil	Nil	Brief Mild Occur less than every 4-6 weeks	More than 80% predicted	Less than 20%
Frequent intermittent	Nil	Nil	More than 2 per month	At least 80% predicted	Less than 20%
Mild persistent	More than once per week but not every day	More than twice per month but not every week	May affect activity and sleep	At least 80% predicted	20%-30%
Moderate persistent	Daily	More than once per week	At least twice per week Restricts activity or affects sleep	60%-80% predicted	More than 30%
Severe presistent	Continual	Frequent	Frequent restricts activity	60% predicted or less	More than 30%

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An individual's asthma pattern (infrequent intermittent, frequent intermittent, mild persistent, moderate persistent or severe persistent) is determined by the level of the table that corresponds to the most severe feature present. Other features associated with that pattern need not be present.
*Predicted values are based on age, sex, and height.
*Difference between morning and evening values.
FEV_1: Forced expiratory volume in 1 second: PEF: Peak expiratory flow.

15. Plethysmography

Patients with chronic persistent asthma may have hyperinflation, as evidenced by an increased total lung capacity (TLC) at plethysmography. Increased residual volume (RV) and functional residual capacity (FRC) with normal TLC suggests air trapping. Airway resistance is increased when significant obstruction is present.

16. Bronchial provocation tests

Bronchial provocation tests may be performed to diagnose bronchial hyper-responsiveness (BHR). These tests are performed in specialized laboratories by specially trained personnel

to document airway hyper-responsiveness to substances (eg, methacholine, histamine). Increasing doses of provocation agents are given, and FEV1 is measured. The endpoint is a 20% decrease in FEV1 (PD20). [90-92]

17. Exercise challenge

In a patient with a history of exercise-induced symptoms (eg, cough, wheeze, chest tightness or pain), the diagnosis of asthma can be confirmed with the exercise challenge. In children >6 years old, the procedure involves baseline spirometry followed by exercise on a treadmill or bicycle to a heart rate greater than 60% of the predicted maximum, with monitoring of the electrocardiogram and oxyhemoglobin saturation.93

Spirographic findings and the peak expiratory flow (PEF) rate (PEFR) are determined immediately after the exercise period and at 3 minutes, 5 minutes, 10 minutes, 15 minutes, and 20 minutes after the first measurement. The maximal decrease in lung function is calculated by using the lowest post-exercise and highest pre -exercise values. The reversibility of airway obstruction can be assessed by administering aerosolized bronchodilators.94-95

18. Chest X-ray

Chest X-ray is indicated in the initial work-up of asthmatic patients. Typical findings are hyperinflation and increased bronchial markings, a chest radiograph may reveal evidence of parenchymal disease, atelectasis, pneumonia, congenital anomaly, or a foreign body.

In a patient with an acute asthmatic episode that responds poorly to therapy, a chest radiograph helps in the diagnosis of complications such as pneumothorax or pneumomediastinum.

19. Paranasal sinus and CT scanning

Consider sinus radiography and CT scanning to rule out sinusitis, co-existing with allergic rhinitis and asthma.

20. Blood testing

CBC, Eosinophil counts, total IgE and RAST may be useful when allergic factors are suspected.

21. Skin prick test

Allergy testing can be used to identify allergic factors that may significantly contribute to the asthma. Once identified, environmental factors (eg, dust mites, cockroaches, molds, animal dander) and outdoor factors (eg, pollen, grass, trees, molds) may be controlled or avoided to reduce asthmatic symptoms.

Allergens for skin testing are selected on the basis of suspected or known allergens identified from a detailed environmental history. Antihistamines can suppress the skin test results and should be discontinued for an appropriate period (according to the particular

agent's duration of action) before allergy testing. Topical or systemic corticosteroids do not affect the skin reaction.

22. Fraction of Exhaled Nitric Oxide testing

Measuring the fraction of exhaled nitric oxide (FeNO) has proved useful as a non-invasive marker of airway inflammation, in order to guide adjustment of the dose of inhaled corticosteroids. [96-98]

23. Histologic findings

Asthma is an inflammatory disease characterized by inflammatory cells, vascular congestion, increased vascular permeability, increased tissue volume, and the presence of an exudate.

Eosinophilic infiltration, a universal finding, is considered a major marker of the inflammatory activity of the disease.

Histologic evaluations of the airways in a typical patient reveal infiltration with inflammatory cells, narrowing of airway lumina, bronchial and bronchiolar epithelial denudation, and mucus plugs. [99-104]

Additionally, a patient with severe asthma may have a markedly thickened basement membrane and airway remodeling in the form of subepithelial fibrosis and smooth muscle hypertrophy or hyperplasia.

24. Management

24.1 Goal for therapy

- Control asthma by reducing impairment through prevention of chronic and troublesome symptoms (eg, coughing or breathlessness in the daytime, in the night, or after exertion)
- Maintain near-normal pulmonary function
- Maintain normal activity levels (including exercise and other physical activity and attendance at work or school)
- Reduce the need for a short-acting beta2-agonist (SABA) for quick relief of symptoms (not including prevention of exercise-induced bronchospasm)
- Satisfy patients' and families' expectations for asthma care105

Reduction in risk can be achieved by preventing recurrent exacerbations of asthma and minimizing the need for emergency room visits and hospitalizations, and preventing progressive loss of lung growth and function providing optimal pharmacotherapy with minimal or no adverse effects is important.

24.2 Pharmacologic treatment

Pharmacologic management includes the use of agents for control and agents for relief. Control agents include inhaled corticosteroids, inhaled cromolyn or nedocromil, long acting

bronchodilators, theophylline, leukotriene modifiers, and more recent strategies such as the use of anti-immunoglobulin E (lgE) antibodies (omalizumab). Relief medications include short-acting bronchodilators, systemic corticosteroids, and ipratropium. [106-107]

For all but the most severely affected patients, the ultimate goal is to prevent symptoms, minimize morbidity from acute episodes, and prevent functional and psychological morbidity to provide a healthy (or near healthy) lifestyle appropriate to the age of child. 108

A stepwise approach to pharmacologic therapy is recommended to gain and maintain control of asthma in both the impairment and risk domains. The type, amount, and scheduling of medication is dictated by asthma severity (for initiating therapy) and the level of asthma control (for adjusting therapy). Step-down therapy is essential to identify the minimum medication necessary to maintain control. See table below.

For pharmacotherapy, children with asthma are divided into 3 groups based on age: 0-4 y, 5-11 y, 12 Y and older. [109]

For all patients, quick-relief medications include rapid-acting beta2-agonists as needed for symptoms. The intensity of treatment depends on the severity of symptoms. If rapid acting beta2-agonists are used more than 2 days a week for symptom relief (not including use of rapid-acting beta2-agonists for prevention of exercise induce symptoms), stepping up treatment may be considered. See the stepwise approach to asthma medications in Table 1, below.

Intermittent Asthma	**Persistent Asthma: Daily Medication**					
Age	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
< 5 y	Rapid-acting beta2-agonist prn	Low-dose inhaled corticosteroid (ICS) Alternate regimen: cromolyn or montelukast	Medium-dose ICS	Medium-dose ICS plus either long-acting beta2-agonist (LABA) or montelukast	High-dose ICS plus either LABA or montelukast	High-dose ICS plus either LABA or montelukast; Oral systemic corticosteroid
5-11 y	Rapid-acting beta2-agonist prn	Low-dose ICS Alternate regimen: cromolyn, leukotriene receptor antagonist (LTRA), or theophylline	Either low-dose ICS plus either LABA, LTRA, or theophylline OR Medium-dose	Medium-dose ICS plus LABA Alternate regimen: medium-dose ICS plus either LTRA or theophylline	High-dose ICS plus LABA Alternate regimen: high-dose ICS plus either LABA or theophylline	High-dose ICS plus LABA plus oral systemic corticosteroid Alternate regimen: high-dose ICS plus LRTA or theophylline plus systemic corticosteroid
12 y or older	Rapid-acting beta2-agonist as needed	Low-dose ICS Alternate regimen: cromolyn, LTRA, or theophylline	Low-dose ICS plus LABA OR Medium-dose ICS Alternate regimen: low-dose ICS plus either LTRA, theophylline, or zileuton	Medium-dose ICS plus LABA Alternate regimen: medium-dose ICS plus either LTRA, theophylline, or zileuton	High-dose ICS plus LABA (and consider omalizumab for patients with allergies)	High-dose ICS plus either LABA plus oral corticosteroid (and consider omalizumab for patients with allergies)

Table 1. Stepwise Approach to Asthma Medications

In the Salmeterol Multicenter Asthma Research Trial (SMART), salmeterol use in asthma patients, particularly African Americans, was associated with a small but significantly increased risk of serious asthma-related events. This trial was a large, double-blind, randomized, placebo-controlled, safety trial in which salmeterol 42 mcg twice daily or placebo was added to usual asthma therapy for 28 weeks. [110]

The study was halted following interim analysis of 26,355 participants because patients exposed to salmeterol (n = 13,176) were found to experience a higher rate of fatal asthma events compared with individuals receiving placebo (n = 13,179); the rates were 0.1 % and 0.02%, respectively. This resulted in an estimated 8 excess deaths per 10,000 patients treated with salmeterol. 111

In the post-hoc subgroup analysis, the relative risks of asthma-related deaths were similar among whites and blacks, although the corresponding estimated excess deaths per 10,000 patients exposed to salmeterol were higher among blacks than whites.

A meta-analysis by Salpeter et al found that LABAs increased the risk for asthma related intubations and deaths by 2-fold, even when used in a controlled fashion with concomitant inhaled corticosteroids. However, the absolute number of adverse events remained small. The large pooled trial included 36,588 patients, most of them adults. 112

The US Food and Drug Administration (FDA) has reviewed the data and the issues and has determined that the benefits of LABAs in improving asthma symptoms outweigh the potential risks when LABAs are used appropriately with an asthma controller medication in patients who need the addition of LABAs. The FDA recommends the following measures for improving the safe use of these drugs :

- LABAs should be used long-term only in patients whose asthma cannot be adequately controlled on inhaled steroids 113
- LABAs should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved; patients should then be switched to an asthma controller medication
- Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA to ensure compliance with both medications

Concerns about the safety of long-acting beta2-agonists and resultant drug safety communications create a question as to the course of treatment if asthma is not controlled by inhaled corticosteroidsY4] A study by Lemanske et al addressed this question and concluded that addition of long-acting beta2-agonist was more likely to provide the best response than either inhaled corticosteroids or leukotriene-receptor antagonists. Asthma therapy should be regularly monitored and adjusted accordingly.

A systematic review of 18 placebo-controlled clinical trials evaluating monotherapy with inhaled corticosteroids supports their safety and efficacy in children with asthma. In addition, the data provide new evidence linking inhaled corticosteroids use in children with asthma to improved asthma control. A recent study to assess the effectiveness of an inhaled corticosteroid used as rescue treatment recommends that children with mild persistent asthma should not be treated with rescue albuterol alone and the most effective treatment to prevent exacerbations is daily inhaled corticosteroids. This study suggests that inhaled

corticosteroids as rescue medication with albuterol might be an effective step down strategy, for children as it is more effective at reducing exacerbations than is use of rescue albuterol alone. A recent Cochrane review concluded that more research is needed to assess the effectiveness of increased inhaled corticosteroid doses at the onset of asthma exacerbation]

In children, long-term use of high-dose steroids (systemic or inhaled) may lead to adverse effects, including growth failure. Recent data from the Childhood Asthma Management Program (CAMP) study and results of the long-term use of inhaled steroids (budesonide) suggest that the long-term use of inhaled steroids has no sustained adverse effect on growth in children. 114-116

Low Daily Doses of Inhaled Glucocorticosteroids for Children 5 years and younger	
Drug	Low Daily Dose (µg)
Beclomethasone dipropianate	100
Budesonide MDI+spacer Budesonide nebulized	200 500
Fluticasone propionate	100

GINA Guidelines

Omalizumab is a recombinant humanized IgG1 monoclonal anti-IgE antibody that binds to the IgE molecule at the same epitope on the Fc region that binds to FcεRL, Omalizumab binds to circulating IgE regardless of allergen specificity, forming small, biologically inert IgE-anti-IgE complexes without activating the complement cascade. An 89 to 99 percent reduction in free serum IgE (i.e., IgE not bound to Omalizumab) occurs soon after the administration of omalizumab and low levels persist throughout treatment with appropriate doses. Proof-of-concept studies have shown that Omalizumab reduces both early-and late –phase asthmatic responses after allergen inhalation challenge, has a marked effect on late-phase as compared with early-phase skin responses, decreases eosinophil numbers in sputum and submucosal bronchial specimens and also down-regulates FcεRI on basophils, mast cells, and dendritic cells. A reduction in the expression of FcεRI on basophils and mast cells decreases the binding of circulating IgE, thus, preventing the release of inflammatory mediators. A reduction in the expression of FcεRI on dendritic cells may decrease allergen processing.
Several randomized, double-blind clinical trials compared omalizumab, administered subcutaneously, with placebo.
These trials demonstrated a clinical benefit from Omalizumab, although the specific findings varied. Three of the trials evaluated patients with moderate-t0-severe persistent asthma (requiring doses of inhaled bleclomethasone, or its equivalent, ranging from 168-1200 µg per day). Two of these tree trials included adolescents and adults, and one was a study of children 6-12 years of age. Treatment with Omalizumab as compared with placebo was associated with significantly fewer exacerbations of asthma per patient, and a significantly lower percentage of patients had an exacerbation, the dose of inhaled corticosteroids required to control symptoms was significantly less among patients treated with Omalizumab than among those who received placebo.

A review by Rodrigo et al looked at 8 studies of omalizumab in children with moderateeto-severe asthma and elevated IgE levels. Children treated with omalizumab were more significantly able to reduce their use of rescue inhalers and their inhaled and/or oral steroid dose than patients in the placebo group. Although no significant differences in pulmonary function were observed, patients receiving omalizumab had fewer exacerbations than the

children receiving placebo. These studies lasted a year or less and did not reveal any significant adverse effects of the omalizumab.

Clinical Use
The role of Omalizumab in the management of asthma has not yet been precisely defined. Patients with persistent asthma (defined as asthma with symptoms that occur more than two days a week or nocturnal symptoms that occur more than twice a month) have several treatment options in addition to the use of inhaled β-adrenergic agonist. These include environmental control (i.e., the elimination or minimization of exposure to aeroallergens), pharmacologic control (i.e., the use of inhaled corticosteroids, leukotriene modifiers, or both), and possibly, immunologic control (i.e., immunotherapy for relevant antigens). In addition, evaluation for coexisting conditions such as allergic rhinitis, sinusitis, and gastroesophageal reflux disease may prove beneficial.

Patients who are particularly likely to benefit from the use of Omalizumab include those with evidence of sensitization to perennial aeroallergens who require high doses of inhaled corticosteroids that have a potential for adverse side effects, those with frequent exacerbations of asthma associated with unstable disease and possibly, those with severe symptoms related in part to poor adherence to daily medication. Analysis of pooled data from published clinical trials have indicated that patients who had a response to Omalizumab had a ration of observed to expected forced expiratory volume in one second (FEV1) of less than 65 percent, were taking doses of inhaled corticosteroids equivalent to more than 800 μg of beclomethasone dipropionate per day, and had at least one visit to the emergency department in the past year. Patients requiring daily oral corticosteroids to control their stamina may be less likely to have response to Omalizumab.

A total serum IgE level should be measured in all patients who are being considered for treatment with Omalizumab, because the dose of Omalizumab is determined on the basis of the IgE level and body weight. The recommended dose is 0.016 mg per kilogram of body weight per international unit of IgE every four weeks, administered subcutaneously at either two-week or four-week intervals. This dose is based on the estimated amount of drug that is required to reduce circulating free IgE levels to less than 10 IU per milliliter.

Monitoring of total serum IgE levels during the course of therapy with Omalizumab is not indicated, because these levels will be elevated as a result of the presence of circulating IgE-anti-IgE complexes. No other laboratory tests seems to be necessary, since there have been no clinically significant laboratory abnormalities noted during treatment.

Cost
Omalizumab is considerably more expensive than conventional asthma therapy, with an average of approximately $12,000 per year. This compares with approximate cosets per year of $1,289 for montelukast, $2,160 for the combination of fluticasone dipropionate and salmeterol, $680 for extended-release theophylline.

A randomized trial of omalizumab for asthma in inner-city children showed improved asthma control, elimination of seasonal peaks in asthmatic exacerbations, and reduced need for other medications for asthma control.

25. Delivery devices and best route of administration

In pediatric asthma, inhaled treatment is the cornerstone of asthma management. Inhaler devices currently used to deliver inhaled corticosteroids (ICSs) fall into the following 4 categories:64

- Pressurized metered dose inhaler (pMDI) - Propellant used to dispense steroid when canister is pressed manually
- Dry powder inhaler (DPI) - Does not require hand-breath coordination to operate
- Breath-actuated pMDI - Propellant used to dispense steroid when patient inhales
- Nebulized solution devices

Go to Use of Metered Dose Inhalers, Spacers, and Nebulizers for complete information on this topic.

In pediatric patients, the inhaler device must be chosen on the basis of age, cost, safety, convenience, and efficacy of drug delivery

Based on current research, the preferred device for children younger than 4 years is a pMDI with a valved holding chamber and age-appropriate mask. Children aged 4-6 years should use a pMDI plus a valved holding chamber. Lastly, children older than 6 years can use either a pMDl, a DPI, or a breath-actuated pMDI. For all 3 groups, a nebulizer with a valved holding chamber (and mask in children younger than 4 y) is recommended as alternate therapy.

Valved holding chambers are important. The addition of a valved holding chamber can increase the amount of drug reaching the lungs to 20%. The use of a valved holding chamber helps reduce the amount of drug particles deposited in the oropharynx, thereby helping to reduce systemic and local effects from oral and gastrointestinal absorption.

A Cochrane review on the use of valved holding chambers versus nebulizers for inhaled steroids found no evidence that nebulizers are better than valved holding chamber. Nebulizers are expensive, inconvenient to use, require longer time for administration, require maintenance, and have been shown to have imprecise dosing.

Newer devices such as…. have been associated with a greater efficacy (as evidenced by…). For MDls, chlorofluorocarbon (CFC) propellants (implicated in ozone depletion) have been phased out in favor of the hydrofluoroalkane-134a (HFA) propellant. Surprisingly, the HFA component is more environmentally friendly and has proven to be more effective, due to its smaller aerosol particle size, which results in better drug delivery. MDls with HFA propellant have better deposition of drug in the small airways and greater efficacy at equivalent doses compared with CFC-MDls.[117]

26. Long-term monitoring

Regular follow-up visits are essential to ensure control and appropriate therapeutic adjustments. In general, patients should be assessed every 1-6 months. At every visit, adherence, environmental control, and comorbid conditions should be checked.

If patients have good control of their asthma for at least 3 months, treatment can be stepped down. However, the patient should be reassessed in 2-4 weeks to make sure that control is

maintained with the new regimen. If patients require step 2 asthma medications or higher, consultation with an asthma specialist should be considered.

27. Outpatient visits should include the following

- Interval history of asthmatic complaints, including history of acute episodes (eg, severity, measures and treatment taken, response to therapy)
- History of nocturnal symptoms
- History of symptoms with exercise, and exercise tolerance
- Review of medications, including use of rescue medications
- Review of home-monitoring data (eg, symptom diary, peak flow meter readings, daily treatments)

28. Patient evaluation should include the following

- Assessment for signs of bronchospasm and complications
- Evaluation of associated conditions (eg, allergic rhinitis)
- Pulmonary function testing (in appropriate age group)

Address issues of treatment adherence and avoidance of environmental triggers and irritants.

Long-term asthma care pathways that incorporate the aforementioned factors can serve as roadmaps for ambulatory asthma care and help streamline outpatient care by different providers.

In the author's asthma clinic, a member of the asthma care team sits with each patient to review the written asthma care plan and to write and discuss in detail a rescue plan for acute episodes, which includes instructions about identifying signs of an acute episode, using rescue medications, monitoring, and contacting the asthma care team. These items are reviewed at each visit.

One study using directly observed administration of daily preventive asthma medications by a school nurse showed significantly improved symptoms among urban children with persistent asthma.

29. Control of environmental factors and comorbid conditions

As mentioned above, environmental exposures and irritants can play a strong role in symptom exacerbations. Therefore, in patients who have persistent asthma, the use of skin testing or in vitro testing to assess sensitivity to perennial indoor allergens is important. Once the offending allergens are identified, counsel patients on avoidance from these exposures. In addition, education to avoid tobacco smoke (both first-hand and second-hand exposure) is important for patients with asthma. 118

Lastly, comorbid conditions that may affect asthma must be appropriately managed. These include the following:

- Bronchopulmonary aspergillosis
- Gastroesophageal reflux disease (GERD)

- Obesity
- Obstructive sleep apnea
- Rhinitis
- Sinusitis
- Depression
- Stress

Inactivated influenza vaccine may be helpful in those who are older than 6 months.

30. Education

Patient education continues to be important in all areas of medicine and is particularly important in asthma. Self-management education should focus on teaching patients the importance of recognizing their own their level of control and signs of progressively worsening asthma symptoms.

Both peak flow monitoring and symptom monitoring have been shown to be equally effective; however, peak flow monitoring may be more helpful in cases in which patients have a history of difficulty in perceiving symptoms, a history of severe exacerbations, or moderate-to-severe asthma.

Educational strategies should also focus on environmental control and avoidance strategies and medication use and adherence (eg, correct inhaler techniques and use of other devices).

Using a variety of methods to reinforce educational messages is crucial in patient understanding. Providing written asthma action plans in partnership with the patient (making sure to review the differences between long-term control and quick-relief medications), education through the involvement of other members of the healthcare team (eg, nurses, pharmacists, physicians), and education at all points of care (eg, clinics, hospitals, schools) are examples of various educational tools that are available and valuable for good patient adherence and understanding.

31. Status asthmaticus

Treatment goals for acute severe asthmatic episodes (status asthmaticus) are as follows:

Acute exacerbation of asthma induces the release of inflammatory mediators prime adhesion molecules in the airway epithelium and capillary endothelium, which then allows inflammatory cells, such as eosinophils neutrophils, and basophils, to attach to the epithelium and endothelium and subsequently migrate into the tissues of the airway. Eosinophils release eosinophilic cationic protein (ECP) and major basic protein (MBP). Both ECP and MBP induce deqsquamation of the airway epithelium and expose nerve endings. This interaction promotes further airway hyperresponsiveness in asthma. This inflammatory component may even occur in individuals with mild asthma exacerbation.

- Correction of significant hypoxemia with supplemental oxygen; in severe cases, alveolar hypoventilation requires mechanically assisted ventilation

- Rapid reversal of airflow obstruction with repeated or continuous administration of an inhaled beta2-agonist; early administration of systemic corticosteroids (eg, oral prednisone or intravenous methylprednisolone) is suggested in children with asthma that fails to respond promptly and completely to inhaled beta2-agonists

1. Yes, See British Guidelines on Management of Asthma (revised 2009).
   : second line treatment of acute asthma in children aged over 2 years.
2. Indications for admission to intensive care or high-dependency units include patients requiring ventilator support and those with severe acute or life threatening asthma who are failing to respond to therapy, as evidenced by:
   - Deteriorating PEF
   - Persisting or worsening hypoxia
   - Hypercapnea
   - Arterial blood gas analysis showing fall in pH or rising H+ concentration
   - Exhaustion, feeble respiration
   - Drowsiness, confusion, altered conscious state
   - Respiratory arrest.

Not all patients admitted to the Intensive Care Unit (ICU) need ventilation, but those with worsening hypixia or hypercapnea, drowsiness or uncousciousness and those who have had a respiratory arrest require intermittent positive pressure ventilation, intubation in such patients is very difficult and should ideally be performed by an anaesthetist or ICU consultant.

- Reduction in the likelihood of recurrence of severe airflow obstruction by intensifying therapy: Often, a short course of systemic corticosteroids is helpful 119-120

Achieving these goals requires close monitoring by means of serial clinical assessment and measurement of lung function (in patients of appropriate ages) to quantify the severity of airflow obstruction and its response to treatment. Improvement in FEV1 after 30 minutes of treatment is significantly correlated with a broad range of indices of the severity of asthmatic exacerbations, and repeated measurement of airflow in the emergency department can help reduce unnecessary admissions.

The use of the peak flow rate or FEV1 values, patient's history, current symptoms, and physical findings to guide treatment decisions is helpful in achieving the aforementioned goals. When using the peak expiratory flow (PEF) expressed as a percentage of the patient's best value, the effect of irreversible airflow obstruction should be considered. For example, in a patient whose best peak flow rate is 160 L/min, a decrease of 40% represents severe and potentially life-threatening obstruction.

An Australian study by Vuillermin et al found that asthma severity decreased in school aged children when parents initiated a short course of prednisolone for acute asthma. Children who received parent-initiated prednisolone for episodes of asthma had lower daytime and nighttime asthma scores, reduced risk of health resource use, and reduced school absenteeism compared with children who received placebo.

32. Prevention of asthma

The goal of long-term therapy is to prevent acute exacerbations. The patient should avoid exposure to environmental allergens and irritants that are identified during the evaluation.

Recurrent acute exacerbation of asthma cause the following histoopathological change in the airways. The airways becomes blocked by viscous, tenacious mucus distended lung parenchyma are composed of eosinophils and epithelial cells. There is an increase in smooth airway muscle with hyperplasia and hypertrophy in the major airways. Shedding of the cilated bronchial wall cells, mainly eosinophils. Apart from the bronchial infiltration of eosinophils there is dilatation of the capillary blood cells. The connective tissue in which these vessels lie consists of strands of widely separated collagen.

Numerous vasoactive agents have been found in broncoalveolar lavage of ___ with recurrent acute exacerbation of asthma including cell-derived mediators, such as histamine, the cysteinyl leukotriene, LTC4, LTD4 and LTE4, and PAF, and also neural-derived mediators, e.g. substance P(SP), neurokinin A and B (NKA, NKB), and calcitonin gene-related peptide (CGRP), PAF is a phospholipid that induces neutropenia, bronchocosntriction, and abnormal airway microvascular leakage, possibly through postcapillary venoconstriction in the tracheobroncial circulation. Thus microvascular leakage of plasma is an inflammatory hallmark of paramount relevance n asthma, generally referred to as abnormally increased vascular permeability. A substantially increased number of PAF receptors are reported in the lungs of asthmatic individuals.

33. Dietary adjustments

When a patient has major allergies to dietary products, avoidance of particular foods may help. In the absence of specific food allergies, dietary changes are not necessary. Unless compelling evidence for a specific allergy exists, milk products do not have to be avoided.

34. Consultations

Any patient with high-risk asthma should be referred to a specialist. The following may suggest high risk:

- History of sudden severe exacerbations
- History of prior intubation for asthma
- Admission to an ICU because of asthma
- Two or more hospitalizations for asthma in the past year
- Three or more emergency department visits for asthma in the past year
- Hospitalization or an emergency department visit for asthma within the past month
- Use of 2 or more canisters of inhaled short-acting beta2-agonists per month
- Current use of systemic corticosteroids or recent withdrawal from systemic corticosteroids

Referral to an asthma specialist for consultation or co-management of the patient is also recommended if additional education is needed to improve adherence or if the patient requires step 4 care or higher (step 3 care or higher for children aged 0-4 y). Consider referral if a patient requires step 3 care (step 2 care for children aged 0-4 y) or if additional testing for the role of allergy is indicated.

The choice between a pediatric pulmonologist and an allergist may depend on local availability and practices. A patient with frequent ICU admissions, previous intubation, and a history of complicating factors or comorbidity (eg, cystic fibrosis) should be referred to a

pediatric pulmonologist. When allergies are thought to significantly contribute to the morbidity, an allergist may be helpful.

Consider consultation with an ear, nose, and throat (ENT) specialist for help in managing chronic rhinosinusitis. Consider consultation with a gastroenterologist for help in excluding and/or treating gastroesophageal reflux.

35. Appendix: Specific pharmacologic treatment

35.1 Bronchodilators, Beta2-Agonists

These agents are used to treat bronchospasm in acute asthmatic episodes, and used to prevent bronchospasm associated with exercise-induced asthma or nocturnal asthma. Recent studies have suggested that short-acting beta2-agonists may produce adverse outcomes (eg, decreased peak flow or increased risk of exacerbations) in patients homozygous for arginine (Arg/Arg) at the 16th amino acid position of beta-adrenergic receptor gene compared with patients homozygous for glycine (Gly-Gly). Similar findings are reported for long-acting beta2-agonists, such as salmeterol. 121-122

35.2 Salbutamol sulfate (Proventil HFA, Ventolin HFA, ProAir HFA)

This beta2-agonist is the most commonly used bronchodilator that is available in multiple forms (eg, solution for nebulization, MOl, PO solution, butalin, ventolin, asthalin, salamol, a.o.). This is most commonly used in rescue therapy for acute asthmatic symptoms. Used as needed. Prolonged use: may be associated with tachyphylaxis due to beta2-receptor down regulation and receptor hyposensitivity.

Some MD is/are available as a breath-actuated inhalers. The ease of administration with the breath-actuated devices make it an attractive choice in the treatment of acute symptoms in younger children who otherwise cannot use an ordinary MDl. The Autohaler delivers 200 mcg per actuation.

Terbutalin, a partial beta-2-agonist is short-acting bronchodilator. The inhaled form of terbutalin starts working within 15 minutes and can last for up to 6 hours.

This nonracemic form of beta-2-agonist (albuterol) offers a significant reduction in the adverse effects associated with racemic albuterol (eg, muscle tremors, tachycardia, hyperglycemia, hypokalemia).

The noncarcemic form of albuterol Levabuterol offers a significant reduction in the adverse effects associated with racemic albuterol (eg, muscle tremors, tachycardia, hyperglycemia, Hypokalemia.
The dose may be doubled in acute severe episodes when even a slight increase in the bronchodilator response may make a big difference in the management strategy (eg, in avoiding patient ventilation). It is available as an MDI (45 mcg per actuation) or solution for nebulized inhalation).

35.3 Xopenex

Nonracemic form of albuterol (xopenex), levalbuterol (R isomer) is effective in smaller doses and is reported to have fewer adverse effects (eg, tachycardia, hyperglycemia, hypokalemia). The dose may be doubled in acute severe episodes when even a slight increase in the bronchodilator response may make a big difference in the management strategy (eg, in avoiding patient ventilation). It is available as an MOl (45 mcg per actuation) or solution for nebulized inhalation.

35.4 Long-Acting Beta2-Agonists

Long-acting bronchodilators (LABA) are not used for the treatment of acute bronchospasm. They are used for the preventive treatment of nocturnal asthma or exercise-induced asthmatic symptoms, for example.

There are 2 LABA are available: salmeterol and formoterol. Both are available as combination products with inhaled corticosteroids.

LABA may increase the chance of severe asthma episodes and death when those episodes occur. Most cases have occurred in patients with severe and/or acutely deteriorating asthma; they have also occurred in a few patients with less severe asthma.

LABAs are not considered first-line medications to treat asthma. LABAs should not be used as isolated medications and should be added to the asthma treatment plan only if other medicines do not control asthma, including the use of low- or medium-dose corticosteroids. If used as isolated medication, LABAs should be prescribed by pulmonologist / allergist.

35.5 Salmeterol

This long-acting preparation of a beta2-agonist is used primarily to treat nocturnal or exercise-induced symptoms. It has no anti-inflammatory action and is not indicated in the treatment of acute bronchospastic episodes. It may be used as an adjunct to inhaled corticosteroids to re9uce the potential adverse effects of the steroids. The medication is delivered via a Diskus DPI.

35.6 Formoterol

Formoterol is a long-acting B2-agonist. It is marketed in dry powder inhalation, a metered-dose inhaler, an inhalation solution and oral tablet.

Formoterol relieves bronchospasm by relaxing the smooth muscles of the bronchioles in conditions associated with asthma. They are used for long-term control and prevention of symptoms, especially nocturnal symptoms.

35.7 Methylxanthines

35.7.1 Theophylline

Theophylline is available in short-acting and long-acting formulations. Because of the need to monitor serum concentrations, this agent is used infrequently. The dose and frequency depend on the particular product selected. The actions of theophylline involve:

- relaxing bronchial smooth muscle
- increasing heart muscle contractility and efficiency as a positive inotropic
- increasing heart rate positive chronotrope
- increasing blood pressure
- increasing renal blood flow
- some anti-inflammatory effects
- central nervous system stimulatory effect mainly on medullary respiratory center.123-125

Parenteral methylxanthines (aminophylline, theophylline) may circumvent the dimininshed delivery of aerosolized β-agonists in acute asthma and young children thus augmenting submaximal bronchial smooth-muscle relaxation. Molecular mechanisms specific to theophylline that may be responsible for its beneficial effect include phosphodiesterase enzyme inhibition, adenosine receptor antagonism, enhanced catecholamine secretion, and modulation of transmembrane calcium fluxes in muscle cells. The influence on calcium may be respoinsble for an increase in respiratory muscle contractility and resistance to diaphragmatic fatigue particularly advantageous in asthmatics with early respiratory failure. Methylxanthines may also assume greater importance during β-receptor desensitization where the response to β agonist drugs is attenuated but a response to aminophylline persists. Clinical trials involving submaximal bronchodialation have shown that the benefit from combinations of methylxanthines and β-agnosits are more likely additive and synergistic.

The use of theophylline is complicated by its interaction with other drugs, chiefly cimetidine and phenytoin, erythromycin, ciprofloxacin and fluoroquinolones and that it has a narrow therapeutic index. It can cause nausea, diarrhea, tachycardia, headache, insomnia

35.8 Inhaled corticosteroids

Steroids are the most potent anti-inflammatory agents. Inhaled forms are topically active, poorly absorbed and thus less likely to cause adverse effects. They are used for long-term control of asthma symptoms and airway inflammation. Inhaled forms reduce the need for systemic corticosteroids.

Inhaled steroids block late asthmatic response to allergens; reduce airway hyper responsiveness; inhibit inflammatory process e.g. cytokine production, adhesion protein activation, and inflammatory cell migration and activation; and reverse beta2-receptor downregulation and subsensitivity (in acute asthmatic episodes with LABA use). 126-127

35.8.1 Fluticasone

Fluticasone has extremely potent vasoconstrictive and anti-inflammatory activity. It has a weak hypothalamic-pituitary adrenocortical axis inhibitory potency when applied topically. It is available as an MDl aerosolized product (HFA) or DPI (Diskus).

35.8.2 Budesonide

Budesonide has extremely potent vasoconstrictive and anti-inflammatory activity. It has a weak hypothalamic-pituitary adrenocortical axis inhibitory potency when applied topically. It is available as a DPI, MDI and nebulized susp (ie, Respules).

35.8.3 Beclomethasone

Beclomethasone inhibits bronchoconstriction mechanisms; causes direct smooth muscle relaxation, decrease the number and activity of inflammatory cells, and decreases airway hyperresponsiveness. It is available as MDI.

35.8.4 Ciclesonide

Ciclesonide is an aerosol inhaled corticosteroid indicated for maintenance treatment of asthma as prophylactic therapy in adolescent patients aged 12 y and older. Not indicated for relief of acute bronchospasm.

Corticosteroids have wide range of effects on multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (eg, histamines, eicosanoids, leukotrienes, cytokines) involved in inflammation.

Maximum benefit may not be achieved for 4 wk or longer after initiation of therapy.

After asthma stability is achieved, it is best to titrate to lowest effective dosage to reduce the possibility of adverse effects. For patients who do not adequately respond to the starting dose after 4 wk of therapy, higher doses may provide additional asthma control. It is available as MDI.[127]

35.8.5 Mometasone furoate inhalation powder (Asmanex Twisthaler)

Mometasone is a corticosteroid for inhalation. It is indicated for asthma as prophylactic therapy.

35.9 Systemic corticosteroids

Corticosteroids are the most potent anti-inflammatory used in asthma. Systemic corticosteroids (SCS) are effective in acute asthma, pulmonary function slowly improves beginning within 6-12 hours, SCS reduces to relapse rate and admission ranks. Several studies suggest duration of 3-5 days. The anti-inflammatory effects of corticosteroids are mediated to a major extent via TRANSREPRESSION, while many side-effects are due to TRANSACTIVATION. New generations of corticosteroids are being developed that preferentially induce TRANSREPRESSION with little or no TRANSACTIVATION.

These agents are used for short courses (3-10 d) to gain prompt control of inadequately controlled acute asthmatic episodes. They are also used for long-term prevention of symptoms in severe persistent asthma as well as for suppression, control, and reversal of inflammation. Frequent and repetitive use of beta2-agonists has been associated with beta2-receptor sub-sensitivity and down regulation; these processes are reversed with corticosteroids.

Higher-dose corticosteroids have no advantage in severe asthma exacerbations, and intravenous administration has no advantage over oral therapy, provided that 81 transit time or absorption is not impaired. The usual regimen is to continue frequent multiple daily dosing until the FEV1 or peak expiratory flow (PEF) is 50% of the predicted or personal best values; then, the dose is changed to twice daily. This usually occurs within 48 hours.

35.9.1 Prednisone

An immunosuppressant for the treatment of autoimmune disorders, prednisone may decrease inflammation by reversing increased capillary permeability and suppressing polymorphonuclear neutrophil (PMN) activity.

35.9.2 Methylprednisolone

Methylprednisolone may decrease inflammation by reversing increased capillary permeability and suppressing PMN activity.

35.10 Leukotriene modifiers

Knowledge that leukotrienes cause bronchospasm, increased vascular permeability, mucosal edema, and inflammatory cell infiltration has led to the concept of modifying their action by using pharmacologic agents. These are either 5-lipoxygenase inhibitors or leukotriene-receptor antagonists.

35.11 Leukotriene antagonists

These are drugs that inhibit leukotrienes and thus suppress inflammation. Leukotriene antagonists such as montelukast, zafirlukast are used in asthma to block the actions of leukotrienes, either by inhibition of the cysteinyl-leukotriene type 1 receptors. (Montelukast, Zafirlukast)

35.11.1 Zafirlukast

Zapirlukast is a selective competitive inhibitor of LTD4 and LTE4 receptors.

The leukotriene-antagonist zafirlukast (Accolate), and montelukast (Singulaire) are proving to be effective for long-term prevention of asthma, including exercise-induced asthma and aspirin (or NSAID)-induced asthma. Their anti-inflammatory actions are different from those of steroids.

Studies suggest that montelukast, wheich comes in a chewable tablet, may be particularly useful for managing asthma in small children (ages two to five) with asthma, since they have trouble with inhaled steroids. Zafirlukast may also reduce the severity of cat allergies, regardless of whether or not asthma is also present.

Of some concern are reports of Churg-Satrauss syncrome in a few people taking zafirlukast or montelukast. Churg-Strauss syndrome is very rare, but it causes blood vessel inflammation in the lungs and can be life threatening. Oral steroids quickly resolve the problem. In fact, usually the syndrome has occurred in patients who were tapering off steroids and changing over to the leukotrines-antagonist. Some experts believe that, in such cases, the steroids may simply have masked the presence of the disorder, which then developed when the steroid drugs were withdrawn. Symptoms include severe sinusitis, flu-like symptoms, rash, and numbness in the hands and feet.

35.11.2 Montelukast

The last agent introduced in its class, montelukast has the advantages that it is chewable, it has a once-a-day dosing, and it has no significant adverse effects.

35.11.3 Omalizumab

Omalizumab is a recombinant, DNA-derived, humanized IgG 1K monoclonal antibody that selectively binds to human Immunoglobulin (IgE). Omalizumab's cost is very high as compared with other drugs used for asthma, and hence is mainly prescribed for patients with severe persistent asthma, which can not be controlled even with high doses of corticosteroids like other protein drugs, omalizumab may cause anaphylaxis in 1 to 2 patients per 1000.

35.12 Combination inhaled steroids/Long-Acting Beta2-Agonists

These combinations may de\crease asthma exacerbations when inhaled short-acting beta2-agonists and corticosteroids have failed. Refer to previous discussion in the LABAs section regarding increased risk of severe asthma episodes and death with LABAs. In a recent study, use of combination therapy using fluticasone propionate and salmeterol prolonged time to first severe asthma exacerbation.

Budesonide is an inhaled corticosteroid that alters level of inflammation in airways by inhibiting multiple types of inflammatory cells and decreasing production of cytokines and other mediators involved in the asthmatic response. Available as MDl in 2 strengths; each actuation delivers formoterol 4.5 mcg with either 80 mcg or 160 mcg.

35.12.1 Budesonide and formoterol

Formoterol relieves bronchospasm by relaxing the smooth muscles of the bronchioles in conditions associated with asthma. Budesonide is an inhaled corticosteroid that alters the level of inflammation in airways by inhibiting multiple types of inflammatory cells and decreasing production of cytokines and other mediators involved in the asthmatic response. This combination is available as an MOl in 2 strengths; each actuation delivers formoterol 4.5-mcg with either 80-mcg or 160-mcg of budesonide.

35.12.2 Mometasone and formoterol

This is a combination corticosteroid and LABA metered-dose inhaler. Mometasone elicits local anti-inflammatory effects in the respiratory tract with minimal systemic absorption. Formoterol elicits bronchial smooth muscle relaxation.

This combination is indicated for prevention and maintenance of asthma symptoms in patients inadequately controlled with other asthma controller medications (eg, low-dose to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, including a LABA. Available in 2 strengths; each actuation delivers mometasone/formoterol 100 mcg/5 mcg or 200 mcg/5 mcg.

35.12.3 Fluticasone and salmeterol

This is a combination corticosteroid and LABA metered-dose inhaler. Fluticasone inhibits bronchoconstriction mechanisms, produces direct smooth muscle relaxation, and may

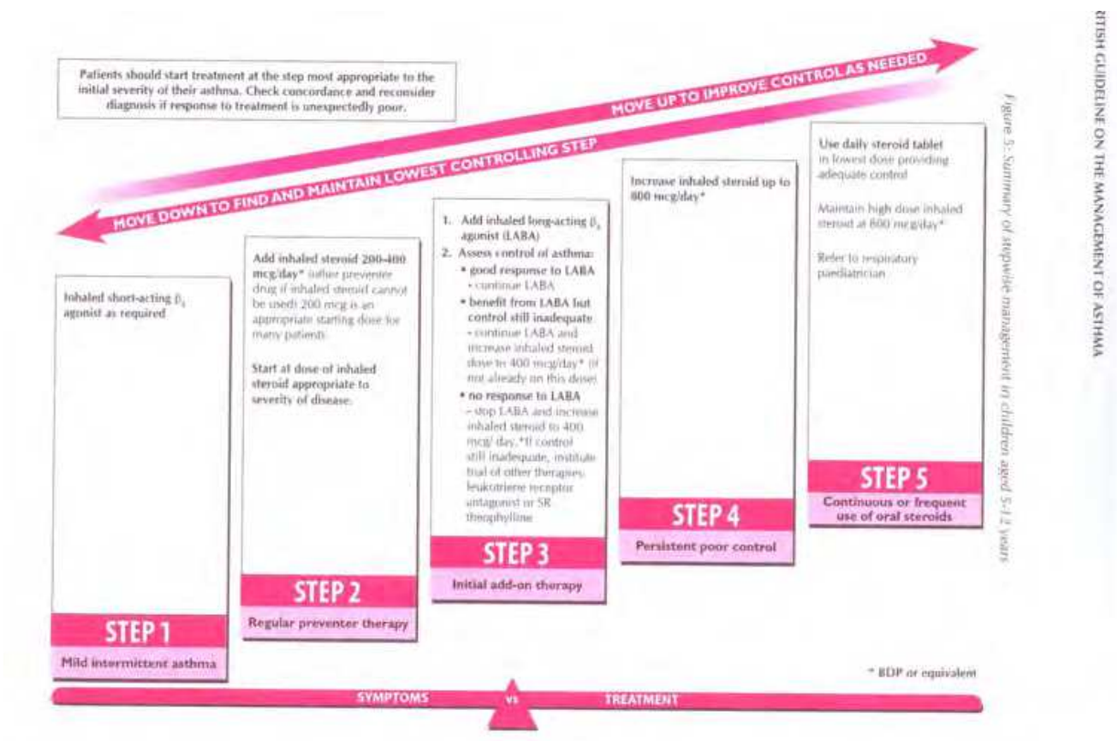
decrease number and activity of inflammatory cells, in turn decreasing airway hyper-responsiveness. It also has vasoconstrictive activity. Salmeterol relaxes the smooth muscles of the bronchioles in conditions associated with bronchitis, emphysema, asthma, or bronchiectasis and can relieve bronchospasms. Its effect may also facilitate expectoration. Adverse effects are more likely to occur when administered at high or more frequent doses than recommended. Two delivery mechanisms are available (ie, powder for inhalation [Diskus], metered-dose inhaler [MDI]). Diskus is available as a combination of salmeterol 50 mcg with fluticasone 100 mcg, 250 mcg, or 500 mcg. The MDI is available as 21 mcg salmeterol with fluticasone 45 mcg, 115 mcg, or 230 mcg.

35.13 Anticholinergic drugs

Anticholinergic drugs are group of bronchodilators that block the neurotransmitter acetylcholine on the muscarinic receptor on bronchial smooth muscle.

35.13.1 Ipratropium bromide

Chemically related to atropine, protropium has antisecretory properties and, when applied locally, inhibits secretions from serous and seromucous glands lining the nasal mucosa. The MDI delivers 17 mcg/actuation. Solution for inhalation contains 500 mcg/2.5 mL (ie, 0.02% solution for nebulization).



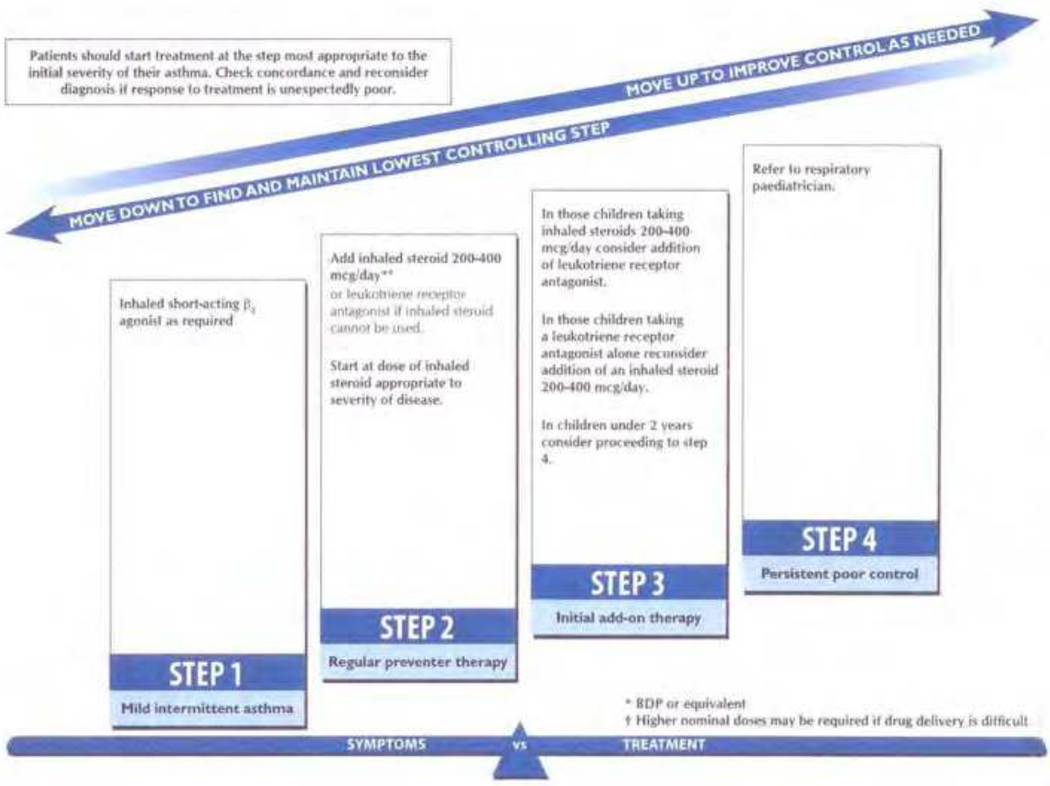


Figure 6. Summary of stepwise management in children less than 5 years

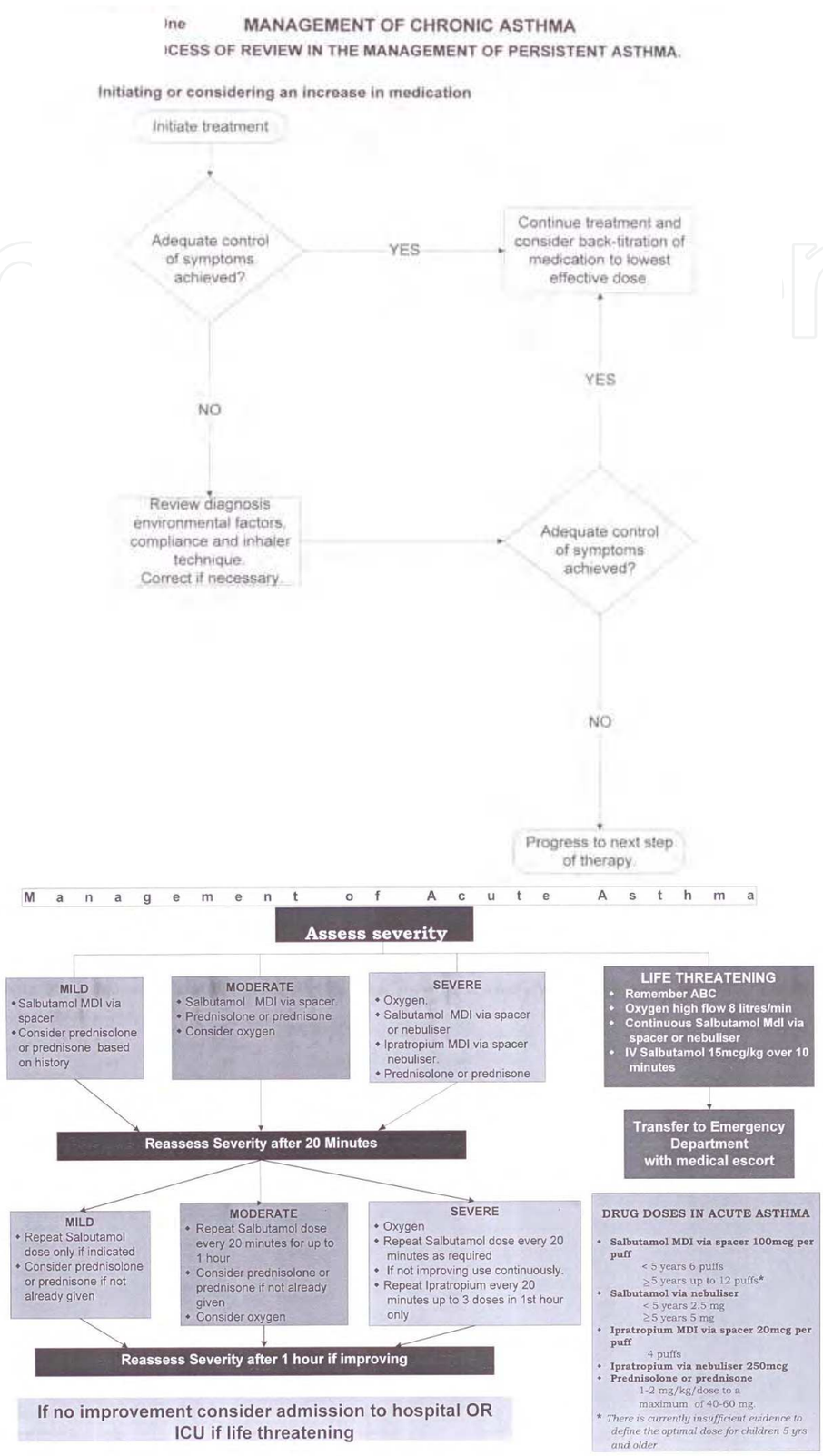
Steroid Therapy

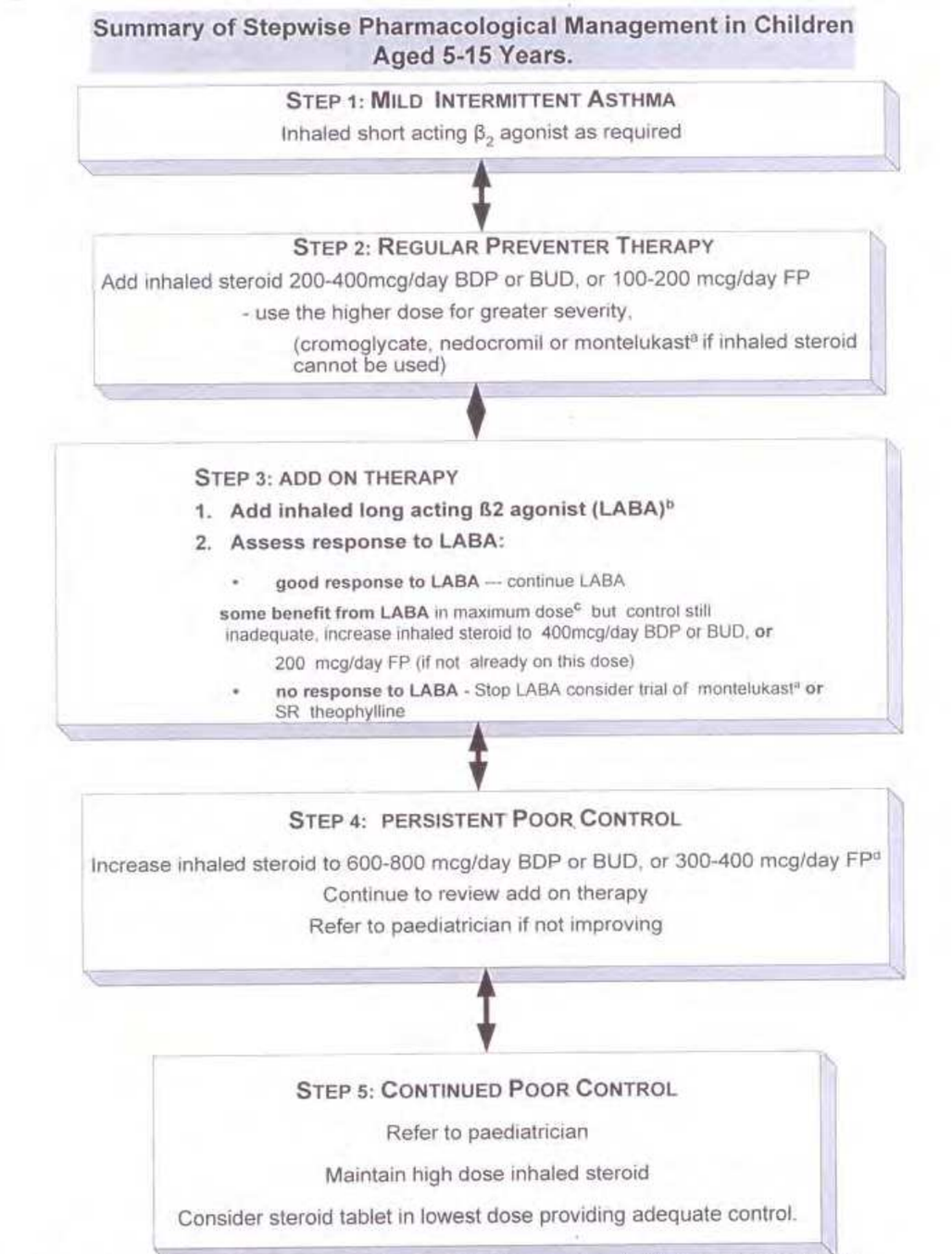
Give prednisolone or prednisone early in the treatment of acute asthma attacks	A
Use a dose of prednisolone or prednisone 1-2mg/kg/day. A maximum dose of 40mg per day is usually sufficient but up to 60mg may be used	☑
Repeat the dose of prednisolone/ prednisone in children who vomit within an hour of the dose, and consider IV steroids hydrocortisone 4mg/kg/dose six hourly	☑
Treatment with systemic steroids for up to three days is usually sufficient, but tailor length of course to the number of days necessary to bring about recovery. Tapering of short courses (up to 7-14 days) of steroids is not necessary.	☑

Inhaled Corticosteroids (ICS)

There is insufficient evidence to support the use of ICS as alternative or additional treatment to steroid tablets for acute asthma. There is no evidence that increasing the dose of ICS is effective in treating acute symptoms, but it is good practice for children already receiving ICS to continue with their usual maintenance doses.

Do not initiate inhaled corticosteroids in preference to steroid tablets to treat acute childhood asthma.	☑
There is no evidence that increasing the dose of inhaled corticosteroid is beneficial in acute attacks of asthma.	☑
Betamethasone (Betnesol) and Dexamethasone are not recommended for use with asthma.	☑


ine MANAGEMENT OF CHRONIC ASTHMA
ICESS OF REVIEW IN THE MANAGEMENT OF PERSISTENT ASTHMA.
Initiating or considering an increase in medication
Initiate treatment
Adequate control of symptoms achieved?
YES
Continue treatment and consider back-titration of medication to lowest effective dose
YES
NO
Review diagnosis environmental factors, compliance and inhaler technique. Correct if necessary.
Adequate control of symptoms achieved?
NO
Progress to next step of therapy.
Management of Acute Asthma
Assess severity
MILD
• Salbutamol MDI via spacer
• Consider prednisolone or prednisone based on history
MODERATE
• Salbutamol MDI via spacer.
• Prednisolone or prednisone
• Consider oxygen
SEVERE
• Oxygen.
• Salbutamol MDI via spacer or nebuliser
• Ipratropium MDI via spacer nebuliser.
• Prednisolone or prednisone
LIFE THREATENING
• Remember ABC
• Oxygen high flow 8 litres/min
• Continuous Salbutamol Mdl via spacer or nebuliser
• IV Salbutamol 15mcg/kg over 10 minutes
Transfer to Emergency Department with medical escort
Reassess Severity after 20 Minutes
MILD
• Repeat Salbutamol dose only if indicated
• Consider prednisolone or prednisone if not already given
MODERATE
• Repeat Salbutamol dose every 20 minutes for up to 1 hour
• Consider prednisolone or prednisone if not already given
• Consider oxygen
SEVERE
• Oxygen
• Repeat Salbutamol dose every 20 minutes as required
• If not improving use continuously.
• Repeat Ipratropium every 20 minutes up to 3 doses in 1st hour only
DRUG DOSES IN ACUTE ASTHMA
• Salbutamol MDI via spacer 100mcg per puff
< 5 years 6 puffs
≥5 years up to 12 puffs*
• Salbutamol via nebuliser
< 5 years 2.5 mg
≥5 years 5 mg
• Ipratropium MDI via spacer 20mcg per puff
4 puffs
• Ipratropium via nebuliser 250mcg
• Prednisolone or prednisone
1-2 mg/kg/dose to a maximum of 40-60 mg.
* There is currently insufficient evidence to define the optimal dose for children 5 yrs and older
Reassess Severity after 1 hour if improving
If no improvement consider admission to hospital OR ICU if life threatening



[a] The only New Zealand Registered Leukotriene Receptor Antagonist, montelukast, is not currently on the Pharmaceutical Schedule

[b] The current Special Authority criteria of the Pharmaceutical schedule allows LABA to be introduced at the higher threshold of 400mcg/day BDP or BUD, or 200mcg/day

[c] Maximum recommended dose of eformoterol is 12mcg bd, and salmeterol 50mcg bd

[d] These levels of ICS are greater than usually required to achieve optimal control (See Dose Response Curve pg 21) and do not hesitate to seek advice from a paediatrician.

ALTERNATIVE DIAGNOSES IN WHEEZY CHILDREN

Clinical clue*	Possible diagnosis*
Perinatal and family history	
• symptoms present from birth or perinatal lung problem	• cystic fibrosis, chronic lung disease of prematurity, ciliary dyskinesia, developmental anomaly
• family history of unusual chest disease	• cystic fibrosis, developmental anomaly, neuromuscular disorder
• persistent sinusitis	• defect of host defence
Symptoms and Signs	
• persistent wet cough	• cystic fibrosis, recurrent aspiration, bronchiectasis, host defence disorder
• excessive vomiting or spilling	• reflux (± aspiration)
• dysphagia	• swallowing problems (± aspiration)
• abnormal voice or cry	• laryngeal problem
• focal signs in the chest	• developmental anomaly, post adenoviral pneumonia, bronchiectasis, tuberculosis
• inspiratory stridor as well as wheeze	• central airway or laryngeal disorder • inhaled foreign body
• failure to thrive	• cystic fibrosis, host defence disorder, gastroesophageal reflux
• clubbing	• bronchiectasis, cystic fibrosis
Chest Xray	
• focal radiological changes	• developmental anomaly, inhaled foreign body, bronchiectasis, tuberculosis, segmental or lobar collapse
• persistent radiological changes	• recurrent aspiration, bronchiectasis,cystic fibrosis

*List not comprehensive

Note: Recurrent cough in the absence of wheeze is unlikely to be due to asthma

ALTERNATIVE DIAGNOSES IN COUGHING CHILDREN

Clinical clue*	Possible diagnosis*
History	
• day care	• recurrent bronchitis
• unimmunised	• pertussis
• symptoms present from birth or perinatal lung problem	• cystic fibrosis, ciliary dyskinesia, developmental anomaly
• family history of unusual chest disease	• cystic fibrosis, developmental anomaly, neuromuscular disorder
• persistent upper respiratory tract disease	• defect of host defence
Symptoms and Signs	
• recurrent cough, asymptomatic between episodes	• recurrent bronchitis, tracheomalacia, mild airway compression
• paroxysmal cough	• pertussis
• persistent wet cough	• cystic fibrosis, recurrent aspiration, bronchiectasis; host defence disorder
• excessive vomiting or spilling	• reflux (± aspiration)
• dysphagia	• swallowing problems (± aspiration)
• abnormal voice or cry	• laryngeal problem
• focal signs in the chest	• developmental anomaly, post adenoviral pneumonia, bronchiectasis, tuberculosis
• inspiratory stridor as well as wheeze	• central airway or laryngeal disorder
• failure to thrive	• cystic fibrosis, host defence disorder; gastroesophageal reflux
• older child	• psychogenic cough, tobacco smoking
• clubbing	• bronchiectasis, cystic fibrosis
Chest Xray	
• focal radiological changes	• developmental anomaly, inhaled foreign body, bronchiectasis, tuberculosis, segmental or lobar collapse
• persistent radiological changes	• recurrent aspiration, bronchiectasis, cystic fibrosis

*List not comprehensive

Source: Management of Asthma in Children aged 1-15 years (Ped. Society of New Zealand)

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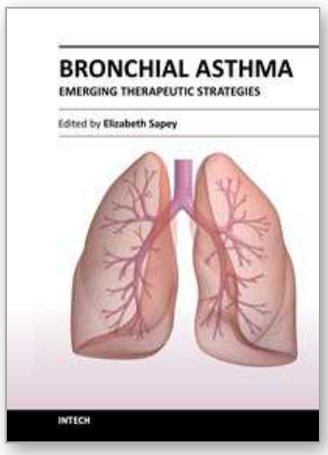

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Asthma remains a serious health concern for millions of people globally. Despite continuing research interest, there have been few advancements that impact clinically on patient care, potentially because asthma has been treated as a homogeneous entity, rather than the heterogeneous condition it is. This book introduces cutting-edge research, which targets specific phenotypes of asthma, highlighting the differences that are present within this disease, and the varying approaches that are utilized to understand it.

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